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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,408	PARIKH ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *12-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☒ Claim(s) *9-11* is/are objected to.

8)☒ Claim(s) *1-17* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/4/05, 3/17/04, &* 9/12/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 are pending.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-11, drawn to methods of managing a respiratory condition, classified in class 600, subclass 532.

II. Claims 12-17, drawn to methods of ensuring a subject with a respiratory condition follows a prescribed treatment protocol, classified in class 700, subclass 702.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are drawn to methods of managing a respiratory condition (Group I) and methods of ensuring a subject with a respiratory condition follows a prescribed treatment protocol (Group II), respectively. The methods of groups I and II are comprise different steps that have different functions and effects.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

During a telephone conversation with Mr. Henry Hyde on October 17, 2005 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-11. Affirmation of this election must be made by applicant in replying to this Office action. Claims 12-17 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

The abstract of the disclosure is objected to because it appears that the word "the" is missing in line 1 and should be inserted between --"for"-- and --"management--". Correction is required. See MPEP § 608.01(b).

The use of the trademark EXHALYZER® D (page 3), PULMICORT®, ADVAIR® (pages 5, 6, 10, and 11) SEVERENT® (page 9), FLORENT® (pages 9 and 11), and PREDNISONE® (page 10) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Claims 9-11 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the necessary required procedure regarding (a) "causing measurement of an analyte in a subject's exhaled breath"; (b) "using said measurement in a function to determine changes to said existing treatment protocol"; and (c) "altering said treatment protocol in accordance with said changes." Independent claim 1 recites steps (a)-(c), shown above, however it is unclear what procedure is involved in "causing a measurement", "using a function," and therefore "altering a treatment protocol" based upon the results of (a) and (b). Clarification of this method by the inclusion of the required necessary steps would help remove any ambiguity concerning the use of the claimed method.

The remaining claims are rejected as being dependent upon a rejected claim.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The internet is a continuously changing medium. For example, URL's that are functional may change in the future and thus no longer correspond to an actual website.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kharitonov et al. (*Monaldi Arch. Chest Dis.*, 1996, *51(6)*, pp 533-537).

Applicant's claims are drawn to a method of managing a respiratory condition in a subject with a pre-existing treatment protocol, comprising the steps of (a) measurement of an analyte in a subject's exhaled breath; (b) using said measurement in a function to determine changes to said existing treatment protocol; and (c) altering said treatment protocol in accordance with said changes; wherein said respiratory condition is asthma (claim 2); wherein said analyte is nitric oxide (claim 3); wherein step (c) comprises changing the frequency of the administration of medication (claim 4); wherein the medicament of claim 3 is inhaled (claim 5); wherein step (c) as modified by claim 3 comprises changing the medication dosage (claim 6); wherein step (c) as modified by claim 3 comprises adding an additional anti-inflammatory medication in addition to those anti-inflammatory medications already part o the existing treatment protocol (claim 7); wherein step (c) as modified by claim 3 comprises removing an anti-inflammatory medication in addition to those anti-inflammatory medications already part o the existing treatment protocol (claim 8); wherein the method of claims 1-8 occurs at least weekly (claim 9); wherein the method of claim 9 occurs daily (claim 10).

Kharitonov teaches that it is known in the art that **exhaled nitric oxide** (NO) is increased in patients with inflammatory diseases of the airways, such as **asthma** and bronchiectasis and **may be modulated by inhaled corticosteroids** (p 533, right hand column, 2nd paragraph, 2nd sentence). Corticosteroids are known medicaments.

Kharitonov suggest that exhaled NO may provide a noninvasive means of monitoring inflammation in the respiratory tract (p 533, right hand column, 3rd paragraph, 1st sentence).

Kharitonov teaches that it is suggested in the art that in inflammatory diseases increases in exhaled NO are due to induction of a third isoform of the NO synthase enzyme (iNOS). It is known in the art that glucocorticoids inhibit the induction of iNOS in epithelial cells *in vitro* and *in vivo*, and reduce exhaled NO levels in **asthmatic patients** to normal (p 534, right hand column, 2nd paragraph, 1st and last sentences and left hand column, 1st paragraph, 1st line).

Kharitonov teaches that regarding asthma, there is now persuasive evidence **that levels of NO are increased in association with airway inflammation and are decreased with anti-inflammatory therapy** (p 535, 1st paragraph, 1st sentence in the section entitled "Clinical Relevance of Exhaled NO" with the sub-heading "Asthma").

Kharitonov teaches it is known in the art that exhaled NO levels are significantly lower in patients with asthma who are treated with **inhaled glucocorticoids**, suggesting inhaled steroids reduce exhaled NO (p 535, left hand column, 2nd paragraph, 1st sentence in the section entitled "Effects of Therapy").

Kharitonov teaches that a double-blind study of **inhaled budesonide**, a synthetic anti-inflammatory corticosteroid, showed a progressive reduction of exhaled NO down to normal values after three weeks of therapy (p 535, left hand column, 2nd paragraph, 4th sentence in the section entitled "Effects of Therapy").

Kharitonov summarizes the state of the prior art by stating that the advantage of exhaled NO is that the measurement is completely non-invasive and **can be performed repeatedly**. In addition, because the measurement is not specific, absolute values are less important than serial

measurements in individual patients. For example, the value of this approach in asthmatic patients has been shown where the dose of the inhaled steroid is changed, resulting in increased levels of NO when the dose is reduced and lower levels of NO when the dose is increased (p 537, right hand column, "Summary" section, 4th, 6th, and 7th sentences).

Kharitonov suggest that the known correlation between exhaled NO levels and anti-inflammatory therapy can be used to monitor whether therapy is adequate, the anti-inflammatory effects of new anti-asthma drugs, and it may facilitate the measurement of dose-response effects with anti-inflammatory treatments (p 537, right hand column, "Summary" section, sentences 8-10).

The following reference is provided to indicate the state of the art and what a person of ordinary skill in the art would have known regarding the administration of pharmaceutical drugs.

Hassan et al. (U.S. Patent application: 2002/0077328) teach that the amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of his invention (COX-2 inhibitor and a vasomodulator) depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, as well as the pharmacokinetic properties of the individual treated, and thus may vary widely. One of skill in the art will appreciate that the dosage regime or therapeutically effective amount of the inhibitor to be administrated may need to be optimized for each individual (paragraph 0301).

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to manage respiratory conditions, including asthma, by measuring analyte

(e.g. NO) in a subject's exhaled breath, using said measurement to ascertain necessary changes in treatment, and altering said treatment accordingly, because (1) it is well known in the art that there is a correlation between exhaled NO levels in a subject's breath and airway inflammation, such as occurs in subjects suffering from asthma; (2) measurement of NO levels are affected by the administration of inhaled steroids; and (3) studies have shown that continued administration of steroids (e.g. budesonide) resulted in a progressive decline of elevated exhaled NO levels in asthmatics to normal levels after three weeks of therapy. A skilled artisan at the time of the instant invention would have known that therapies involving the administration of pharmaceutical agents to a subject may vary widely because said therapies are dependent upon many factors, including age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, the particular compound(s) employed, as well as the pharmacokinetic properties of the individual treated. A person of ordinary skill in the art active in the management of a respiratory condition at the time of the instant invention would have known that methods of appropriately tailoring a therapeutic regimen to the symptoms and needs of a given patient could involve changing medicament dosages, the frequency of administration of pharmaceutical agents, and the addition or removal of drugs used in said therapeutic treatment. A person of ordinary skill at the time of the instant invention would have been motivated to use Kharitonov's teachings and suggestions because the monitoring of exhaled NO is a completely noninvasive method of managing a respiratory condition, it can be performed repeatedly, and it has been suggested as a method of evaluating whether a therapy is adequate, monitoring the anti-inflammatory effects of new anti-asthma drugs, and it may facilitate the measurement of dose-response effects with anti-inflammatory treatments.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kharitonov et al. (*Monaldi Arch. Chest Dis.*, 1996, *51(6)*, pp 533-537) in view of Information for Transcriptionists (MedicalNotes.com), 2001-04-10 [online] [retrieved on 2005-10-18] Retrieved from the Internet Archive database <URL: http://web.archive.org/web/20010410235147/http://www.medicalnotes.com/TranscriptionInfo.htm />.

Applicant's claims 1-10 have been described *supra*. Claim 11 is drawn to the method of claim 10 wherein the method additionally comprises uploading data from said measurement of the subject's exhaled nitric oxide concentration to a clinician using the internet.

The teachings of Kharitonov have been set forth above.

MedicalNotes.com's website describes that their service objective is to make uploading transcriptions to their website as quick and easy as possible. Medical records using this service are uploaded to a database of medical records and can be confidentially and securely accessed using the Internet. Data regarding the clinical related measurements (e.g. measurement of a subject's exhaled NO) are considered part of a subject's medical record, and hence the limitations of claim 11 would have been obvious to a person of ordinary skill aware of MedicalNote.com's database service.

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Kharitonov and the services of MedicalNotes.com to affect the uploading of medical data (i.e. a subject's measured exhaled NO concentration) to a clinician using the internet. A skilled artisan would have been motivated to use MedicalNotes.com's disclosed service to upload a subject's measured exhaled NO concentration

data because a subject's medical records would be confidentially and securely uploaded to a website on the internet from which a clinician using the internet would be able to access said records.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Silkoff et al. (U.S. Patent No. 6,010,459).

Applicant's claims have been described *supra*.

Silkoff teaches the **measurement of exhaled substances** may be useful as a **diagnostic** and **prognostic tool** in a variety of medical conditions for a wide variety of medical conditions. For example, when assessing pulmonary function it is desirable to measure the levels of exhaled endogenous gases (e.g. **nitric oxide**) (column 2, lines 29-35).

Silkoff teaches that it is art-recognized that **asthmatic patients** have relatively high exhaled NO levels compared to normal subjects and **these levels decrease rapidly after the institution of anti-inflammatory treatment** (column 2, lines 23-26).

Silkoff states that methods according to his invention are eminently suitable for both the inpatient and outpatient setting, because **these methods are reproducible, quick**, and easy to perform by medical staff and comfortable for the subject so that a pulmonary exhaled breath measurement system could become a routine part of the lung function assessment in every respirology clinic (column 3, lines 32-36).

Silkoff teaches a method for **measuring components of exhaled breath of a subject**, preferably measuring **exhaled nitric oxide** (column 3, lines 40-41 and line 35).

Silkoff teaches an apparatus that provides a device for measuring the components of exhaled breath of a subject (column 4, lines 18-20). Such an apparatus could be used to affect or cause the measurement of analytes in a subject's exhaled breath, including nitric oxide (NO).

Silkoff does not teach using the results of a subject's exhaled breath measurements to determine changes to existing treatment protocols or to alter existing treatment protocols in accordance with said changes, however, the Examiner contends that this would have been obvious, as discussed below.

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to use Silkoff's methods in conjunction with his claimed device to measure NO levels in an asthmatic subject's breath, because it is well known in the art that asthmatic patients have relatively high exhaled NO levels compared to normal subjects. It is also well known in the art that anti-inflammatory treatments of asthmatic patients may result in a reduction of NO levels to normal. A skilled artisan would have been motivated to use Silkoff's methods and device because these are reproducible, quick, easy to perform by medical staff, and comfortable for the subject. A skilled artisan would also have appreciated that reproducible and easy to perform methods could be used to measure a subject's exhaled breath repeatedly, as needed. A person of ordinary skill in the art would have known that anti-inflammatory treatment of asthmatic patients reduces levels of exhaled NO in a subject's breath; and would have been motivated to modify the anti-inflammatory drug or drugs used, drug dosages, and the frequency of administration of said drugs in said patient's treatment protocol to optimize the effectiveness of treatment in light of the specific needs and symptoms of a given patient. Therefore, a person of ordinary skill in the art would have had a reasonable expectation of successfully managing asthma by measuring a

subject's exhaled breath NO levels per Silkoff's method/device, incorporating an anti-inflammatory therapy into said subject's treatment protocol, and altering the treatment protocol as appropriate.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaston et al. (U.S. patent No. 6,033,368) in view of Kharitonov et al. (*The Lancet* 1994, *343*, pp 133-135).

Applicant's claims have been described *supra*.

Gaston teaches a condensate colorimetric nitrogen oxide analyzer that determines the content of nitrogen oxides in exhaled breath condensate (column 1, lines 5-7).

Gaston teaches it has been shown that endogenous production of **nitrogen oxide** in the human airway is increased in patients with **asthma** and other inflammatory lung diseases (column 1, lines 30-32).

Gaston teaches that his analyzer useful in both clinical and domiciliary settings for inexpensive evaluation of asthma as demonstrated by Gaston et al. (column 2, lines 59-63 and Examples 1 and 2).

Gaston lacks in the teaching of using the results of a subject's exhaled breath measurements to determine changes to existing treatment protocols, altering existing treatment protocols in accordance with said changes, and using anti-inflammatory therapy to treat asthmatics.

Kharitonov et al. teach a method directed to **managing a respiratory condition** (asthma) in individuals using **exhaled breath NO measurements** (page 133, left hand column, Summary, last paragraph).

Kharitonov identifies the **inhalation of steroids** with a quantitative reduction of exhaled NO and discloses that "exhaled NO concentrations are significantly higher than normal in patients with **asthma** who are not receiving inhaled steroids" (page 134, right hand column, Discussion section, 2nd paragraph in said section).

Kharitonov suggests that the measurement of exhaled NO may be a **means of detecting and monitoring airway inflammation** and **assessing** anti-inflammatory treatments. The measurement of exhaled NO is simple, non-invasive, can be repeated, and is possible in children and patients with severe disease (p. 134, right hand column, Discussion section, 4th paragraph).

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to use Gaston's device to measure NO levels in an asthmatic person's breath, because it is known in the art that endogenous production of nitrogen oxide in the human airway is increased in patients with asthma and other inflammatory lung diseases. It is also known in the art (Kharitonov, p 134) that the inhalation of steroids by asthmatic patients leads to a reduction of NO levels to normal. A skilled artisan would have been motivated to use Gaston's device in view of Kharitonov's teachings to manage asthma by measuring exhaled NO because the measurement of NO is simple, non-invasive, repeatable, and can be used with children and patients with severe disease. A skilled artisan would have appreciated that the measurement of NO could be repeated as often as was deemed clinically necessary (i.e. daily, weekly, etc). A person of ordinary skill in the art would have been motivated to modify the anti-inflammatory drug or drugs used, drug dosages, and the frequency of administration of said drugs in said patient's treatment protocol to optimize the effectiveness of treatment in light of the specific needs and symptoms of a given patient. Therefore, a person of ordinary skill in the art would

have had a reasonable expectation of successfully managing asthma by measuring a subject's exhaled breath NO levels using Gaston's device in view of Kharitonov's teachings, incorporating an anti-inflammatory therapy into said subject's treatment protocol, and altering the treatment protocol as appropriate.

Conclusion

The specification is objected to because of the improper use of trademarks. Claims 12-17 are withdrawn as being drawn to a non-elected group. Claims 9-11 are objected to as being in improper form. Claims 1-11 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James H. Alstrum-Acevedo, Ph. D.

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SUPERVISORY PATENT EXAMINER